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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/609,383	07/03/00	HEINEGARD	D 06803.0008

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EXAMINER	
HUYNH, P	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/609,383	Applicant(s) HEINEGARD ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *9-22 and 25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,23,24 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-35 are pending.

2. Applicant's election with traverse of Group I, Claims 1-8, filed 8/17/01, is acknowledged. Upon reconsideration and in response to applicant's election with traverse to the restriction requirement separating the analog of SEQ ID NO: 2 of Group II and the homolog of SEQ ID NO: 2 of Group III, the prior art search has been extended to cover Groups I, II and III (now Claims 1-8, 23-24 and 35) that reads on a purified or isolated peptide is CILP, analog of a CILP, a homolog of CILP or a fragment of a CILP thereof, a pharmaceutical composition comprising said CILP, an acceptable physiological carrier and a kit comprising said CILP. Therefore, the requirement of Groups IV-XXXII are still deemed proper and is therefore made FINAL.

3. Claims 9-22 and 25-34 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-8, 23-24 and 35 that read on CILP, an analog of CILP, a homolog of CILP and fragment of a CILP are being acted upon in this Office Action.

5. The drawings, filed 7/3/00, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 23-24 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified or isolated human peptide of SEQ ID NO: 2 wherein the peptide is a human cartilage intermediate layer protein (CILP) and fragments of a human CILP selected from the group consisting of SEQ ID NO: 3-17 and 21-22 for making antibody (pages 27 and 49) and for detection assay (page 30), does not reasonably provide enablement for a purified or isolated peptide wherein the peptide is (1) *any* analog of a CILP, (2)

any homolog of a CILP, (3) *any* mammalian CILP peptide such as a dog peptide, a cat peptide, and a rodent peptide, (4) *any* fragment of a CILP, (5) *any* fragment of an analog of a CILP, (6) *any* fragment of a homolog of a CILP wherein said fragment is immunoreactive with at least one antibody that is specific for a CILP, an analog of a CILP, or a homolog of a CILP for treating individual suffering from joint diseases such as OA, rheumatoid arthritis, crystal deposit arthritis, psoriatic arthritis and reactive arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a purified or isolated human peptide of SEQ ID NO: 2 wherein the peptide is a cartilage intermediate layer protein (CILP) and fragments of a human CILP selected from the group consisting of SEQ ID NO: 3-17 and 21-22.

Other than the specific human CILP peptide and fragments mentioned above for antibody production and detection assay, the specification fails to provide any guidance as how to make and use *any* isolated peptide wherein the CILP peptide is any mammalian CILP peptide, *any* analog of *any* CILP, *any* homolog of a CILP and *any* fragment thereof for a pharmaceutical composition for treating any arthritis disease mentioned above. The transitional phrase "comprising" is open-end. It expands the peptide to include additional amino acid residues at either end. There is no guidance as to which amino acids within the full-length amino acid sequence (peptide) of SEQ ID NO: 2 can be add, delete, the type and number of amino acids within the amino acid sequence (peptide) of SEQ ID NO: 2 can be substitute and that after addition, deletion or substitution of amino acids would retain the structure and function of SEQ ID NO: 2, in turn, can be use for treating any disease such as arthritis.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are

critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 2 that after substitution, deletion, insertion and/or modification will retain both structure and have similar function is unpredictable. It follows that any analog, homolog and fragment thereof are not enabled.

Claims 23 and 24 recite "a pharmaceutical composition" comprising a cartilage intermediate layer protein (CILP), an analog of a CILP, a homolog of a CILP or a fragment thereof wherein the fragment is immunoreactive with at least one antibody that is specific for a CILP, an analog of a CILP or a homolog of a CILP. However, the specification fails to provide any *in vivo* data, working examples, or guidance with respect to dosages as to treat a patient suffering from any disease such as arthritis using any peptide mentioned above. A "pharmaceutical composition" in the absence of in vivo data is unpredictable for the following reasons: (1) efficacy of the peptide has not been definitively demonstrated; (2) it is not always possible to extrapolate directly from in vitro experiments such as binding of peptide to any CILP antibody to in vivo studies; (3) adverse reactions from the recipient may result.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

8. Claims 1-8, 23-24 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* analog of a CILP, (2) *any* homolog of a CILP, (3) *any* mammalian CILP peptide such as a dog peptide, a cat peptide, and a rodent peptide, (4) *any* fragment of a CILP, (5) *any* fragment of an analog of a CILP, (6) *any* fragment of a homolog of a CILP wherein said fragment is immunoreactive with at least one antibody that is specific for a CILP, an analog of a CILP, or a homolog of a CILP.

The specification discloses only a purified or isolated human peptide of SEQ ID NO: 2 wherein the peptide is a cartilage intermediate layer protein (CILP) and fragments of a human

CILP selected from the group consisting of SEQ ID NO: 3-17 and 21-22 for making antibody (pages 27 and 49) and for detection assay (page 30).

With the exception of human CILP peptide of SEQ ID NO: 2 and fragments of human CILP peptides of SEQ ID NO: 3-17 and 21-22, there is insufficient written description of the structure associated with functions of any isolated or purified mentioned above.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "at least one antibody" in claims 1 and 7 is ambiguous and indefinite because it is not clear which antibody that is specific for a CLIP.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Lorenzo *et al* (J Bio Chem 273(36): 23469-75, Sept 1998; PTO 1449).

Lorenzo *et al* teach a purified or isolated cartilage intermediate layer protein (CILP) from human articular cartilage which is a chondrocyte-containing tissues wherein the peptide is a mammalian peptide that is 100% identical to the claimed peptide of SEQ ID NO: 2 (See page 23469, column 2 Materials and Methods, Fig 2 on page 23472, in particular). Lorenzo *et al* further teach said CILP protein has 1184 amino acids with a calculated molecular mass of 132.5 kDa (See page 23472, column 1, in particular) and a fragment of a CILP (See Table 1, in particular). The reference teaches a fragment comprising a sequence that is immunoreactive with at least one antibody that is specific for CILP comprising the amino acid sequence of the reference peptide apart from an extra COOH-terminal cysteine residue spanning amino acid residues 704-722 corresponding to the human homologous NH-2 terminal of NTPPHase of Fig 2 (See page 23471, Antibodies, in particular). Lorenzo *et al* teach that carboxyl terminal of the reference human CILP has 90% similarity to a porcine ectonucleotide pyrophosphohydrolase, NTPPHase which is a homolog of a CILP (See page 23472, column 2, Similarity to other protein, in particular). The reference peptide can be made recombinantly (See page 23473, column 1, Expression and processing of the precursor protein, in particular). The reference also teaches a synthetic peptide EDRTFLVGNLEIRERRLFNC of Fig 5B which is a fragment of a CILP and also an analog of a human homologous NH2-terminal of NTPPHase (See page 23471, column 1, page 23473, column 1, last paragraph, Fig 5B, in particular). Thus, the reference teachings anticipate the claimed invention.

13. Claims 1-2 and 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Masuda *et al* (Gene 197: 277-287, Sept 1997; PTO 892).

Masuda *et al* teach a purified or isolated porcine NTPPHase protein or recombinant peptide from porcine chondrocyte, which is a homolog of a cartilage intermediate layer protein (CILP) (See page 282, reference sequence, in particular). The protein has 599 amino acids (See page 281, column 1, last paragraph, in particular) which is a carboxyl-terminal fragment of NTPPHase (See page 285, column 2 line 1-2, in particular) and the reference fragment is immunoreactive with at least one antibody that is specific for a CILP (See page 285 and Fig 5B of Gene 197: 277-287, in particular) and as disclosed on page 51, lines 2-4 and page 42 line12-15 of instant specification. Thus, the reference teachings anticipate the claimed invention.

14. Claims 1-7, 23-24 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,876,963 (March 1999; PTO 892).

The '963 patent teaches a purified or isolated polypeptide (peptide) of human (which is a mammal) pyrophosphohydrolase-1 (NTPPH-1) wherein the polypeptide is a homolog of a cartilage intermediate layer protein (CILP) and the reference polypeptide is a fragment of the claimed peptide which has 99.7% identity to the claimed peptide of SEQ ID NO: 2 (See Figs 1A-H, SEQ ID NO: 1 of '963, column 9, lines 40-61, in particular). The reference peptide is isolated from human articular cartilage (See column 9 line 60-61, in particular). The '963 patent further teaches the method of making the reference polypeptide or fragments thereof using the reference polynucleotide recombinantly (See column 12, lines 16-55, column 17 lines 8-43, in particular). The '963 patent teaches a pharmaceutical composition comprising the reference polypeptide and fragment thereof and a pharmaceutical acceptable carrier (See column 22, lines 4-6, bridging column 23, lines 1-36, in particular) and a kit wherein the reference polypeptide is place in an appropriate container along with the all necessary reagents (See column 23, lines 37-41). Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-7, 23-24 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 6,124,095 (filed Dec 1997; PTO 892).

The '095 patent teaches a purified or isolated polypeptide (peptide) of human (which is a mammal) pyrophosphohydrolase-2 (NTPPH-2) wherein the polypeptide is a homolog of a cartilage intermediate layer protein (CILP) and the reference polypeptide is a fragment which has 99.7% identity to the claimed peptide of SEQ ID NO: 2 (See Figs 2A-C, SEQ ID NO: 3 of '095, in particular). The reference polypeptide is isolated from human osteoarthritic synovial chondrocyte (See column 11 line 26-27, in particular). The '095 patent further teaches the method of making the reference polypeptide or fragments thereof using the reference polynucleotide recombinantly (See column 14, lines 59-67, in particular). The '095 patent teaches a pharmaceutical composition comprising the reference polypeptide and fragment thereof and a pharmaceutical acceptable carrier (See column 23, lines 34-60, in particular) and a kit wherein the reference polypeptide is place in an appropriate container along with the all necessary reagents (See column 25, lines 5-9). Thus, the reference teachings anticipate the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorenzo *et al* (J Bio Chem 273(36): 23469-75, Sept 1998; PTO 1449) or Masuda *et al* (Gene 197: 277-287, Sept 1997; PTO 892) each in view of US Pat No. 5,876,963 (March 1999; PTO 892) or US Pat No. 6,124,095 (filed Dec 1997; PTO 892).

The teachings of Lorenzo *et al* and Masuda *et al* have been discussed supra.

The claimed invention in claim 35 differs from the teachings only by the recitation of a kit comprising a cartilage intermediate layer protein (CILP) in a physiologically acceptable carrier and necessary reagents to administer the CILP.

The '963 patent teaches a kit comprising the human pyrophosphohydrolase-1 (NTPPH-1), which is a homolog of a cartilage intermediate layer protein (CILP) and a pharmaceutical carrier placed in an appropriate container along with the all necessary reagents (See Figs 1A-H, SEQ ID NO: 1 of '963, column 9, lines 40-61, column 23, lines 37-41, in particular).

The '095 patent teaches a kit comprising the purified human pyrophosphohydrolase-2 (NTPPH-2), which is a homolog of a cartilage intermediate layer protein (CILP) and a pharmaceutical carrier placed in an appropriate container along with the all necessary reagents (See column 23, lines 34-60, column 25, lines 5-9, in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute the NTPPH-1 polypeptide as taught by the '963 patent or the NTPPH-2 polypeptide as taught by the '095 patent for the CILP peptide as taught by Lorenzo *et al* or Masuda *et al* in a kit as taught by the '963 patent and the '095 patent.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to do this for commercial expediency since the kit contains all the necessary reagents as taught by the '963 patent (see column 23, lines 37-41, in particular) and the '095 patent (see column 25, lines 5-9, in particular).

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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